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Evidence of a Locus for Schizophrenia and Related Disorders on the Short Arm of Chromosome 5 in a Large Pedigree

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We attempted to identify a locus for schizophrenia and related disorders in 24 nuclear families of schizophrenic probands using a predefined classification system for affected cases that included those disorders most clearly identified as sharing a genetic relationship with schizophrenia—schizoaffective disorder and schizotypal personality disorder. Initially, we evaluated 8 markers on chromosome 5 on the first 12 families with available genotyping and diagnostic assessments and, assuming autosomal dominant transmission, found a lod score of 2.67 for the D5S111 locus (5p14.1-13.1) in one large nuclear family (no. 17; sibship: n = 12; schizophrenia: n = 3; schizotypal personality disorder: n = 2); the other 11 families were much smaller, less complete, and provided little additional information. Other branches of no. 17 were then assessed and the 2-point lod score for family 17 rose to 3.72; using multipoint analysis the lod score in 17 was 4.37. When only schizophrenia was used to define affectedness, the positive evidence for linkage to D5S111 was greatly reduced. Sensitivity analysis indicated that the lod score is heavily dependent upon the predefined diagnostic criteria. Our studies of other families of schizophrenic probands eventually totalled 23, but linkage to D5S111 in these yielded a −2.41 lod score. The results provide evidence for genetic linkage of the D5S111 locus to schizophrenia and related disorders in one family. It may be of interest that over several generations, almost all the ancestors of family 17 could be traced back to a small, relatively isolated, hill region of Puerto Rico.

KEY WORDS: schizophrenia, schizoaffective disorder, schizotypal personality disorder, linkage analysis, family study

INTRODUCTION

Despite evidence for genetic factors in schizophrenia and related disorders [Kety et al., 1975], no genetic linkage marker or candidate gene has been confirmed [Kendler and Diehl, 1993]. To achieve statistical power most linkage studies have employed large families with several chronic schizophrenic members. However, previous studies of biological relatives of patients with schizophrenia indicate that a genetic trait underlying the transmission of schizophrenia within families is not limited to schizophrenia alone, but includes other phenomenologically related, although sometimes less severe disorders [Kety et al., 1975; Kendler and Gruenberg, 1984; Baron et al., 1985; Frangos et al., 1985; Gershon et al., 1988; Kendler et al., 1993c]. For this reason, an alternative approach to linkage studies in schizophrenia is to use an expanded phenotype which encompasses disorders that have been shown by twin, adoption, and family studies to bear a genetic relationship to schizophrenia [Keefe et al., 1991].

A relationship between schizophrenia and schizoaffective disorder is evident, especially when the latter disorder is defined, as in DSM-III-R (American Psychiatric Association, 1987) or -IV (American Psychiatric Association, 1994), to include only those with schizophrenia-like psychotic symptoms that persist in the absence of major affective symptoms [Baron et al., 1982]. Relatives of schizophrenic probands have been repeatedly observed at greater risk for schizoaffective disorder

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than relatives of normal controls [Gershon et al., 1988; Kendler et al., 1985, 1993d; Maier et al., 1993; Baron et al., 1982], and the relatives of schizoaffective disorder probands have shown a greater risk of schizophrenia compared to relatives of controls [Kendler et al., 1986, 1993a; Maier et al., 1993]. In addition, adoption study data indicate comparable risks of schizophrenia in biologic relatives of schizophrenic and schizoaffective adoptees [Kendler and Gruenberg, 1984].

In addition to schizoaffective disorder, another good candidate for inclusion in the definition of the schizophrenia-related phenotype is schizotypal personality disorder (SPD). Adoption and family studies have provided strong evidence for a genetic relationship between schizophrenia and SPD [Kendler et al., 1981b, 1993c, 1994; Kendler, 1985, 1988; Frangos et al., 1985; Gershon et al., 1988; Maier et al., 1993]. Certain specific SPD features suggest a closer genetic relationship to schizophrenia than others [Ingraham, 1995; Webb and Levinson, 1993]. An analysis of Provincial Sample of the Danish Adoption Study found suspiciousness, flat or spotty affectivity, and seclusive withdrawn behavior most frequent among the nonschizophrenic biologic relatives of schizophrenic adoptees and each feature was significantly more common than among the biologic relatives of controls. Psychotic-like symptoms, on the other hand, were not more prevalent among the biologic relatives of the schizophrenic adoptees than controls [Ingraham, 1995]. Several family studies have observed that, in contrast to positive psychotic-like SPD symptoms, the negative SPD traits, primarily reflecting social and cognitive deficits [Gunderson et al., 1983; Kendler, 1985; Torgersen et al., 1993; Webb and Levinson, 1993; Maier et al., 1994], better characterized the biologic relatives of schizophrenic probands compared to those of normal controls or other comparison groups. A study of twins from a nonclinical population [Kendler et al., 1991] found that the positive and negative symptoms associated with SPD represent 2 relatively independent, strongly heritable dimensions. However, only negative symptoms were related to other characteristics also associated with genetic factors in schizophrenia—trait anhedonia [Grove et al., 1991], attentional dysfunction [Grove et al., 1991; Cornblatt and Erlenmeyer-Kimling, 1985], and poor eye-tracking [Grove et al., 1991; Holzman et al., 1988].

In the present study, we examined linkage of genetic markers to this broadened phenotype for schizophrenia and related disorders. For our first investigations, genetic markers on chromosome 5 were chosen. Early reports from Bassatt et al. [1988] and Sherrington et al. [1988] suggested that loci on the long arm of chromosome 5 might be related to the expression of schizophrenia [Bassatt et al., 1988; Sherrington et al., 1988], although subsequent studies, including one from Sherrington et al. [1988] could not confirm this [Kennedy et al., 1988; St. Clair et al., 1989; Hallmayer et al., 1992; Macciardi et al., 1992; Detera-Wadleigh et al., 1989; Aschauer et al., 1990; McGuffin et al., 1990; Kaufman et al., 1989; Gurling, 1994]. Overall, less attention has been focused on the short arm of chromosome 5, but while some studies have rejected linkage to various loci there [Kennedy et al., 1989; Coon et al., 1994], a carrier of a normal balanced chromosome 5 translocation (5:14), including sections from both arms around the centromere (p14.1:q32.3), produced 5 offspring, 2 of whom had a partial 5p trisomy, one with schizophrenia the other with refractory epilepsy [Malaspina et al., 1992]. We report evidence for linkage to the D5S111 locus (5p14.1-p13.1) and other markers on the short arm of chromosome 5 in one large kindred, whose members were diagnosed using strictly defined predetermined criteria for the schizophrenia-related phenotype.

MATERIALS AND METHODS

Ascertainment and Diagnosis of Schizophrenic Probands

The family histories of patients with chronic schizophrenia as well as patients with other psychiatric disorders who were admitted to the research programs of the Mt. Sinai School of Medicine were routinely evaluated blind to proband diagnosis and without prior knowledge of family structure [Silverman et al., 1993]. All schizophrenic probands were diagnosed using Schedule for Affective Disorder and Schizophrenia [SADS; Endicott and Spitzer, 1978] and met both Research Diagnostic Criteria [RDC; Spitzer et al., 1972] and DSM-III-R [American Psychiatric Association, 1987] criteria for schizophrenia. The first-degree relatives of the probands were identified and individually evaluated for the disorders included in the Family History RDC [Andreasen et al., 1977] and several personality disorder traits including schizophrenia-related personality [Kendler et al., 1984]. Families were recruited for the direct family study in several ways: through schizophrenic probands participating in clinical research protocols with a known positive family history for schizophrenia or related disorders (N = 8), or they were selected at random, hence, without reference to family history (n = 9), or through a referral to the family studies program by clinicians or interested family members (n = 7). In this third group, a schizophrenic family member was arbitrarily designated the proband and given a SADS interview to ensure a schizophrenia diagnosis by RDC and DSM-III-R criteria. Families of psychiatric patients without schizophrenia or normals were also recruited and studied to enable assessment of family members blind to the proband diagnosis. The present study is thus derived from the family members of the first 24 families of schizophrenic probands providing informed consent with available diagnostic and genetic information.

Assessment of Relatives

Face-to-face interviews with all available living first-degree adult relatives of schizophrenic probands and controls were conducted using the SADS-Lifetime (SADS-L) version or, most recently, a modified version of the Comprehensive Assessement of Symptoms and History [CASH; Andreasen, 1985] supplemented by sections of the SADS-L. In addition, all nonpsychotic relatives were also interviewed with the Structured Interview for Diagnosing DSM-III-R Personality Disor-

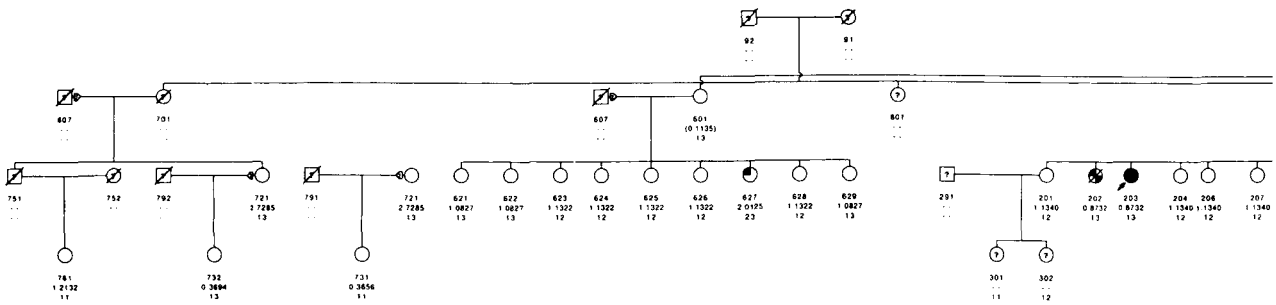

Fig. 1. Pedigree no. 17 showing the proband and other individuals with schizophrenia (fully filled), DSM-III-R SPD (lower right quadrant filled), and SPD-FS (upper left quadrant filled); no cases of SAD were diagnosed. Open symbols are assessed individuals classified as unaffected. Question marks reflect individuals not assessed and thus classified as unknown. The numbers under each relative are the identification numbers (line 1), the results of the sensitivity analysis (line 2) and the genotype for D5S111 (line 3). The sensitivity analysis result indicates the decrease or increase if the number is in parentheses, from 3.72, the maximum lod score obtained, when the relative's diagnosis was changed. To protect confidentiality, we changed most males (squares) to females (circles).

ders [SIDP-R; Stangl et al., 1985]. Finally, the Supplemental Questions for Assessing Schizotypal Symptoms [S-QuASS; Silverman et al., 1995] was integrated into the SIDP-R interview. The S-QuASS interview includes questions, some selected from the Structured Interview for Schizotypy [SIS; Kendler, 1989] pertaining to the type and quality of schizotypal symptoms [Siever et al., 1995]. The diagnostic interviews took approximately 5 or 6 hours for each relative. To supplement the information obtained from the face-to-face interviews, informant interviews were also employed on every relative. Informants were also interviewed using the SADS, SIDP-R, and the S-QuASS. When complete, the direct and informant diagnosticians met to compare ratings, share the information collected, note discrepant ratings, and reach a preliminary consensus rating based on all available information. With 3 exceptions, relatives of probands who could not be assessed in face-to-face interviews were not included in the study. For the 3 exceptions, medical records were obtained for one relative with psychiatric hospitalizations, and informants were extensively interviewed using the SADS, SIDP-R, and S-QuASS. For every relative studied, a narrative description was written using all available information and the final diagnosis was established at a consensus meeting led by L.J.S. All personnel involved with the diagnosis of relatives were blind to the proband diagnosis and genetic marker data.

Diagnostic Criteria

Criteria used to classify relatives as affected were defined prior to the start of the study and used without modification. Relatives were considered affected if they met diagnostic criteria for one of the following: 1) schizophrenia, as defined by DSM-III-R or RDC; 2) DSM-III-R schizoaffective disorder (SAD) or RDC SAD, mainly schizophrenic; 3) either DSM-III-R SPD or DSM-III-R SPD criteria modified for family studies (SPD-FS). The SPD-FS criteria require the presence of 4 rather than 5 *total* DSM-III-R SPD items. However, at least 2 SPD symptoms must not be positive or psychotic-like. These criteria were selected because nonpsychotic-like symptoms (SPD items 5–9), which emphasize social deficits of SPD, appear to be more familial and closely related to schizophrenia [Kendler et al., 1981b, 1991; Gunderson et al., 1983; Kendler, 1985; Ingraham, 1995; Webb and Levinson, 1993]. Relatives who did not meet these criteria were classified as unaffected whether or not they met criteria for other psychiatric disorders. Relatives not assessed were classified as unknown.

Genetic Marker Typing

High molecular weight DNA was isolated from whole blood as described by Lahiri and Nurnberger [1991]. Genetic marker typing was done by polymerase chain reaction (PCR) amplification of microsatellite CA/GT repeat sequences [Lahiri and Nurnberger, 1991]. Chromosome 5-specific CA/GT repeat primer sequences were obtained from the Genome Data Base using sequences provided by Weber et al. [1991] and Weissenbach et al. [1992]. The primers were designed to have similar annealing temperatures which allowed uniform PCR conditions. The 5′ end of the positive strand primer was labeled with ^{32}P using γ-^{32}P-ATP and T4 kinase. The PCR products were separated by polyacrylamide gel electrophoresis under denaturing conditions (8 M urea, 32% formamide) and detected by autoradiography. Markers were oriented on the chromosome using the Cooperative Human Linkage Center (CHLC) consensus map of chromosome 5. Individuals in the genotyping laboratory were blind to all diagnostic information.

Analysis Methods

We had planned to investigate multiple modes of transmission [Hodge and Elston, 1994]. Since we were using only one definition of the schizophrenia-related phenotype that was expanded as far as could be firmly justified by genetic epidemiological studies, we were prepared to examine a range of high penetrance levels (50–90%). For each marker, at least 20 unrelated individuals and as many as 60 were analyzed to determine the number of alleles and allele frequency. The frequency of the disease gene was estimated to be 0.006.

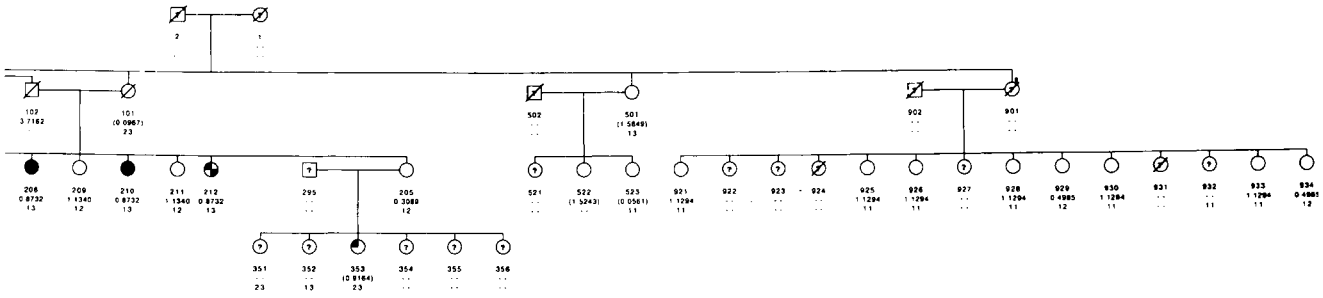

Fig. 1. (*continued*)

This frequency yields a prevalence for schizophrenia and related disorders of approximately 1%. The 2-point linkage analysis was carried out using LIPED [Ott, 1985]. We used FASTMAP [Curtis and Gurling, 1993] for multipoint linkage analysis in order to examine the consistency of results between a marker of interest and other markers in the general region but at some distance away. Marker typing was checked for incompatibilities at each locus investigated on chromosome 5. Only at the time of analysis were the pedigree and diagnostic data combined in pedigree files.

RESULTS

Linkage Results

Our initial analysis with 8 chromosome 5 markers included the members of 12 families of schizophrenic probands. The combined lod scores from all 12 families provided evidence against tight linkage (lod scores <-2.0 at 0.01 recombination fraction) for 5 loci (D5S209, D5S210, D5S211, D5S117, D5S208). For one locus, D5S111, assuming autosomal dominant transmission with no phenocopies [Durner and Greenberg, 1995], we found a maximum lod score of 3.26 at a recombination fraction of 0.01 and penetrance of 90%. Upon inspection of the individual families, it was apparent that one family, no. 17 of Puerto Rican origin (see Fig. 1), accounted for most of the positive lod score (2.67). The nuclear family (the 200 series in Fig. 1), with 12 offspring, had 3 children affected with schizophrenia and 2 with SPD (as defined by DSM-III-R and our modified criteria, SPD-FS). We then chose to expand this family. Twenty-seven additional relatives from the extended family were interviewed and genotyped. Two of these (nos. 627 and 353) were classified as affected (both with SPD-FS). In total, 7 individuals were classified as affected (mean age of affecteds: 36.7 ± 8.1 years, range: 26–47). There were no cases of schizoaffective disorder in family 17. The relatives classified as unaffected in this family had a mean age of 40.3 ± 15.4 years with a range of 20–78. Analysis of the full family assuming autosomal dominant inheritance and penetrance of 90% gave a maximum lod score of 3.72 ($\theta = 0.01$) with D5S111. The only obligate recombinant at D5S111 was person 205, who while unaffected, had an offspring who met criteria for SPD-FS. Assuming a recessive mode of transmission gave a maximum lod score of 2.2. The difference between lod scores associated with dominant and recessive modes of transmission was significant ($\Delta = 1.51$, $P < .05$) [Greenberg and Berger, 1994]. A linkage analysis for the D5S111 locus using only schizophrenia as affected and all other diagnosed cases as unaffected, using the same penetrance and gene frequencies, gave a maximum lod score of 0.67.

Interestingly, in family 17, D5S111 is not highly polymorphic (4 alleles; frequency: 0.10, 0.40, 0.48, 0.02). By chance, it is almost fully informative in the original nuclear family and in the cousin sibship, where the only person classified as affected (SPD-FS, no. 627) was also the only one to inherit the 3 allele from the sib of one of the proband's parents (who also carried the 3 allele). Thus, despite the lack of a large number of polymorphisms for this marker, we had almost the maximal amount of information. However, since incorrect marker allele frequencies can lead to incorrect lod scores [Freimer et al., 1993], we varied the marker allele frequencies. No combination of changes produced lod score changes of more than approximately 0.5 lod score units. As discussed below, family 17 is descended from many generations of ancestors who lived in a rural, hill region of Puerto Rico. We re-estimated the allele frequency of D5S111 using 40 unrelated, healthy individuals from this region and found a similar distribution of the D5S111 allele (frequencies: 0.14, 0.25, 0.59, 0.02). The lod score using these allele frequencies was 3.78.

In the initial analysis we assumed that the gene frequency for the schizophrenia-related phenotype was 0.006. Changing the gene frequency from 0.06 to 0.0006 gave maximum lod scores from 3.9 to 3.6 ($\theta = 0.01$), respectively. Thus, the lod score result is relatively insensitive to the assumed disease allele frequency.

Linkage results can also be affected by the penetrance level assumed. In the first analysis of the D5S111 locus using the available relatives from the first 12 families studied, the 90% penetrance gave the maximum lod score. Although for schizophrenia, that level is high, our expansion of the phenotype to include apparently more common manifestations of the schizophrenia-related phenotype supported using a higher level than for schizophrenia alone. In the subsequent analyses of family 17 including the extended pedigree, we maintained the 90% level. However, in subsidiary analyses to examine the effect of the penetrance assumption, we systematically lowered the penetrance to 50%, in 10% decrements. The maximum lod scores for 80%, 70%, 60%, and 50% penetrances were 3.32, 2.96, 2.62, and

2.29, respectively. When we conducted an analysis using only the affected cases, the lod score was 0.72.

Sensitivity Analysis

To determine the effects of a change in the diagnosis of individuals, we did a sensitivity analysis on family 17 using people in the pedigree who were assessed and genotyped [Hodge and Greenberg, 1992]. This analysis involves recalculating the lod score after changing the affectedness status in a single relative in the pedigree to its opposite (e.g., a relative originally classified as affected would be reclassified as unaffected). This procedure is conducted for each relative included in the original analysis. The results of the sensitivity analysis (*Fig. 1, line 2*) show that changing the diagnosis of people in the pedigree in most cases (36/41) led to a drop in the lod score of between 0.31 and 3.72. The mean change in lod score was 1.07 and the mode was 1.13. Changing the diagnosis of one of the parents in the original nuclear family, no. 102, leads to the largest drop (3.72). In 5 cases, indicated on Figure 1 by numbers in parentheses, a change in diagnosis caused an increase in the lod score.

Multipoint Analysis

Lod scores for the other markers in this region of chromosome 5 were mostly positive, but at relatively large recombination fractions (Table I). We used FASTMAP [Curtis and Gurling, 1993] to obtain a multipoint lod score. Loci D5S419, D5S395, D5S76, D5S418, and D5S430 were fixed at locations relative to each other according to the CHLC map of chromosome 5 (available through the Internet). D5S76, originally assigned to the long arm of chromosome 5 [Weissenbach et al., 1992], is between D5S419 and D5S395 on the CHLC map. The exact positions of D5S111 and D5S108 are not known, but the best map position of D5S111 is between D5S419 and D5S76 and the best map position of D5S108 is between D5S419 and D5S418. We fixed the position of D5S111 midway between D5S419 and D5S76 and D5S108 midway between D5S76 and D5S395. Slight variations in the positions of these loci negligibly affected the results. The maximum multipoint lod score with a penetrance of 0.90 was 4.37 at the location of D5S111 (Fig. 2).

Follow-Up Study on Other Families of Schizophrenic Probands

Concurrent to our study of the extended pedigree of family 17, we continued to study families of other schizophrenic probands. Table II shows the number of relatives in each, the number of relatives assessed for diagnosis and D5S111 genotyping, the number of affected family members, and the associated lod score at $\theta = 0.01$ using a 0.006 gene frequency and a 90% penetrance, that is, the same as used for family 17. Although excluding 17, this table includes the original 11 other families first studied, but additional relatives were later assessed and genotyped in these families. The combined lod score in these 23 families, not including 17, was −2.14. Using the full sample of 24 families, i.e., including family 17, we conducted a test of heterogeneity that was not significant ($\chi^2 = 3.00$, d.f. = 1, n.s.).

Examination of Additional Markers Close to D5S111

The alleles of newly available markers (D5S651, D5S674, and D5S477), which have more polymorphisms, were also examined in family 17. Two of these markers (D5S477 and D5S651) showed a zero recombination with D5S111 in family 17, i.e., their segregation exactly matched the segregation of the D5S111 alleles. For D5S674, one relative, classified as unaffected, showed a recombination with D5S111. Lod scores for these markers were similar to those for D5S111 (D5S651: lod score = 3.98, $\theta = .01$; D5S477: lod score = 3.99, $\theta = .01$; D5S674: lod score = 3.90, $\theta = .05$). The new markers gave slightly different scores from D5S111 because they were somewhat more informative than D5S111. D5S674 gave a slightly lower lod score than the other 2 new markers used because of the recombinant (with those markers and D5S111) in the unaffected relative noted above.

Unremarkable Clinical Characteristics of Affected Cases in Family 17

No unusual clinical features were identified in family 17. The 3 cases of schizophrenia were typical with respect to onset (~early 20s), clinical picture (both positive and negative symptoms), and course. The relatives with SPD all had prominent social deficit, negative symptoms, although positive, psychotic-like symptoms were also present.

Origins of Family 17

As noted above, family 17 was one of the very few in our series that was of Puerto Rican ancestry. The proband was originally ascertained at the Mt. Sinai

TABLE I. Family No. 17 Lod Scores for Markers at 5p(14.1-13)

	Recombination fraction ($\theta_m = \theta_f$)						
Marker	0.00	0.01	0.05	0.10	0.20	0.30	0.40
D5S419	−5.2972	−0.1755	0.7309	1.1200	1.2623	0.9877	0.4505
D5S111	3.6833	3.7162	3.7007	3.4999	2.8011	1.8609	0.7650
D5S76	−3.4351	−0.9631	−0.2688	−0.0117	0.1287	0.0975	0.0284
D5S108	−5.1532	0.2001	0.9830	1.2786	1.3200	0.9962	0.4418
D5S395	2.2243	2.1840	2.0197	1.8069	1.3510	0.8471	0.3167
D5S418	−4.6174	−1.2077	0.2508	0.8022	1.0660	0.8580	0.3829
D5S430	−8.0154	−0.7195	0.6328	1.0977	1.2470	0.9641	0.4316

Medical Center and the first-degree relatives lived in New York City at the time of study. However, the proband's parents and all their offspring were born in and around a relatively isolated, rural hill region of Puerto Rico near the Montañas de Corozal with little inward migration [Vazquez Calzada, 1981]. Through extensive interviews with older members of the family, we examined the genealogy of family 17 and found that, for at least 3 prior generations, almost all of the proband's direct ancestors were born in the same region. Still earlier generations were identified as native to Puerto Rico, and were presumed to be from the same region, but no more specific information about them was available.

DISCUSSION

Our results provide evidence for genetic linkage at locus D5S111 (5p14.1-p13.1) with schizophrenia and related disorders in one large pedigree assuming an autosomal dominant inheritance. Newer, more polymorphic markers in the same region as D5S111 gave consistent results. In addition, the analysis of other more distant markers in the vicinity of D5S111 also show heritability consistent with the inheritance of D5S111. Thus, the lod score in family 17 cannot be due to incorrect typing or "unlucky" genotypes of markers for the few critical untyped individuals. The evidence for linkage in family 17 under an autosomal recessive transmission gave significantly weaker evidence compared to the autosomal dominant. The sensitivity analysis showed that the linkage results could change dramatically if the diagnosis of any one of a number of individuals was changed. The overall lod score for the other 23 nuclear families tested provided evidence against linkage for the D5S111 locus. The range of lod scores in these other families, however, was at modest levels and none yielded lod scores beyond 1.00 in either a positive or negative direction. These families were much smaller than 17, and all had fewer affected cases. In addition, many of these families were essentially uninformative at the D5S111 locus. For these reasons it was not surprising that the evidence for heterogeneity was not significant. Nevertheless, the combined negative lod score in the 23 families suggests a schizophrenia causing locus at D5S111 in family 17, if indeed present, is rare.

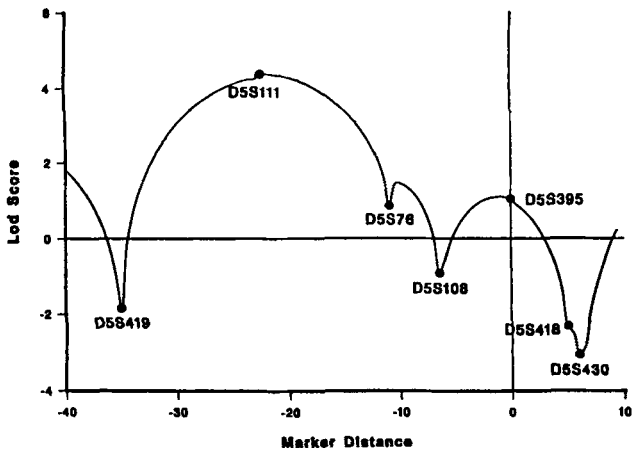

Fig. 2. Multipoint analysis of schizophrenia for the markers on chromosome 5p using FASTMAP. The map positions are taken from the CHLC map, except for the positions of D5S111 and D5S108, which are estimated. The maximum lod score is 4.37.

The evidence for linkage in family 17 resulted from a diagnostic strategy which a priori determined the presence of schizophrenia or a predetermined set of related disorders as the criterion for classification as affected. This criterion was based on the available genetic epidemiological data, especially investigations able to control for environmental factors (i.e., adoption and twin studies). One of the most compelling sources of evidence implicating genetic factors in the etiology of schizophrenia is provided by the Danish Adoption Study [Kety et al., 1975]. In the original Copenhagen sample, the evidence for genetic factors depended entirely on the inclusion of subjects with uncertain or latent schizophrenia (later used to formulate criteria for SPD [Spitzer et al., 1979]); only when these subjects were included within the "schizophrenia spectrum" was a statistically significant increase of schizophrenia-related disorders observed in the biologic relatives of schizophrenic adoptees. Subsequent family, twin, and adoption studies have confirmed the familial/genetic relationship of schizophrenia and SPD [Baron et al., 1985; Kendler, 1988; Kendler et al., 1993c; Onstad et al., 1991] and indicate that the social deficit-related SPD symptoms possess a stronger genetic relationship to schizophrenia than psychotic-like symptoms [Gunderson et al., 1983; Kendler, 1985; Torgersen et al., 1993; Ingraham, 1995; Webb and Levinson, 1993; Kendler et al., 1984, 1991; Maier et al., 1994].

A greater presence of SPD features have also sometimes been found in families of probands with affective disorder. In a high-risk study, the number of adolescents with prominent DSM-III SPD features (i.e., 3+) was greater among both offspring of parents with schizophrenia and offspring of parents with affective disorder compared to those of normal parents [Squires-Wheeler et al., 1988]. However, in the largest and most definitive epidemiologic study of the first-degree relatives of schizophrenic and other psychiatric probands, conducted in Roscommon County, Ireland [Kendler et al., 1993c], SPD was significantly more common among relatives of schizophrenic probands compared to both relatives of affective disorder probands and relatives of general population controls, while the latter 2 groups had quite similar, low rates of SPD. The presence of a major affective disorder and other psychiatric disorders has sometimes been used to classify relatives as affected in linkage studies of schizophrenia [Sherrington et al., 1988; St. Clair et al., 1989; Hallmayer et al., 1992; Detera-Wadleigh et al., 1989; Aschauer et al., 1990]. These disorders were not used to categorize relatives in the present study, however, since the preponderance of genetic epidemiological evidence does not suggest a genetic relationship with schizophrenia [Baron et al., 1985; Frangos et al., 1985; Onstad et al., 1991; Kendler et al., 1981a, 1982, 1985, 1993b; Wender et al., 1986; Wiessman et al., 1984]. Thus, in addition to

TABLE II. D5S111 Linkage Analysis Results in 23 Other Families

	Family members			Number of schizophrenia-related disorders				
Family	Total relatives	Alive	Interviewed	Total	Schizophrenic	Schizoaffective	SPD/FS-SPD	Lod score[a] D5S111
1	8	6	6	4	4	0	0	−0.0002
2	8	8	5	3	1	0	2	−0.6559
6	10	9	7	2	1	1	0	−0.1684
13	7	7	6	5	1	0	4	−0.1501
15	7	6	6	2	2	0	0	0.0004
16	4	3	2	2	1	0	1	0.0010
18	5	5	5	2	1	0	1	0.0878
21	5	3	4	2	1	0	1	−0.3407
22	6	6	6	1	1	0	0	−0.4470
23	15	15	10	1	1	0	0	−0.8945
28	12	11	7	2	2	0	0	−0.4471
30	8	5	5	3	1	1	1	−0.0324
31	12	11	7	1	1	0	0	0.2156
32	7	6	5	1	1	0	0	−0.4472
35	6	4	4	1	1	0	0	0.2447
37	5	4	4	1	1	0	0	−0.0933
41	8	8	5	1	1	0	0	0.6376
48	9	8	6	3	1	0	2	−0.0183
50	8	8	6	2	1	0	1	−0.2732
65	9	8	5	2	1	0	1	0.5069
68	6	6	6	1	1	0	0	−0.0263
79	4	3	3	1	1	0	0	−0.0590
81	5	4	4	2	1	0	1	−0.0546
Total	174	154	124	45	28	2	15	−2.4142

[a]Gene frequency = 0.006; penetrance = 0.90.

schizophrenia, we decided at the outset of our family study to classify as affected only relatives who met DSM-III-R criteria for schizoaffective disorder or SPD or our modified schizotypal criteria (SPD-FS) based on the presence of the nonpsychotic-like, social deficit features. This scheme provided us with the broadest version of schizophrenia-related phenotype that can be justified based on the available genetic epidemiological evidence. Broadening the phenotype in this way enabled us to assume an increased penetrance in the families studied; using schizophrenia alone to classify relatives yielded only weak, albeit positive, evidence for linkage.

The choice of marker and gene allele frequencies and penetrance used in a linkage analysis can potentially influence the lod score obtained and the original allele frequencies used in these analysis were derived from a non-Puerto Rican sample [Freimer et al., 1993]. In the case of family 17, however, varying the allele frequency had minimal effect on the results. Furthermore, reestimating the allele frequency, based on a pool of unrelated individuals coming from the same region as family 17, did not change the results.

We chose an estimated gene frequency of 0.006 because it yielded a prevalence for schizophrenia and related disorders of about 1%. Our choice may seem somewhat low, since the lifetime risk of schizophrenia alone is usually estimated to be 1%, but given the likely genetic heterogeneity and nongenetic forms of this illness, any single gene is unlikely to account for all observed schizophrenia. Thus, 0.006 is a plausible gene frequency estimate. In any case, varying the gene frequency by a factor of 10 in either direction (0.06 and 0.0006) had little affect on the lod score.

The 90% penetrance level gave the maximum lod score when only the nuclear family had been ascertained and analyzed. The same high penetrance was maintained in subsequent analyses of the extended pedigree and subsidiary analyses revealed that it continued to give the maximum lod score. A 90% penetrance is high, but the decision to expand the phenotypic boundaries beyond schizophrenia to include schizoaffective disorder and SPD means that we are, in effect, increasing the penetrance. This was confirmed when we examined the cosegregation of the marker allele and the affected phenotypes in family 17. With one exception, every person who was designated as affected also carried the marker and all but 3 people designated as normal, did not carry the marker. This translates into a high penetrance for this form of schizophrenia and related disorders. Estimates of penetrance for schizophrenia are based on identical twin studies, sibs, etc., which, in the case of schizophrenia, are drawn from a heterogeneous disease population. Population estimates of penetrance, however, may have little bearing on a particular disease form. The specific form of schizophrenia that we are investigating may be, as would be consistent with our results, highly penetrant, at least when schizotypals are counted as affected.

The use of a high penetrance means that the evidence for linkage in family 17 depends almost as much on unaffected members as it does on those classified as affected. In an analysis which emphasizes affected members, such as a sib pair analysis, one assumes only

that all the affected members have the same condition. The use of a high penetrance attaches the additional constraint that the unaffected members are unaffected, not because they are nonpenetrant but because they are not carrying the gene. This allows us to gain information from the unaffected members as well as the affected members. Had there been more relatives in family 17 carrying the marker but lacking the phenotype, evidence against linkage would have been the result.

One of the markers used in our multipoint analysis, D5S76, had previously been reported to be linked to schizophrenia [Sherrington et al., 1988], but was mapped to the long arm, rather than the short arm of chromosome 5. It was thus surprising that the CHLC had mapped D5S76 to the short arm of chromosome 5. We obtained intermarker lod scores for D5S76 and the other markers on the short arm of chromosome 5 and confirmed that they were linked. The published studies of chromosome 5 and schizophrenia involved the restriction fragment length polymorphism (RFLP) marker that identified D5S76. Since we used the PCR marker, it may be that the PCR and RFLP markers are in fact different, located in different regions on chromosome 5, or that our work represents a confirmation of the finding reported by Sherrington et al. [1988]. We do not believe that, at this time, it is possible to fully understand what is the true location of D5S76—nor is it germane to our results. The main nuclear family of no. 17 is uninformative for D5S76. Had the D5S76 locus not been examined in family 17, the results of the multipoint analysis using all the other markers would be virtually unaffected.

Our results provide evidence for genetic linkage at locus D5S111 (5p14.1-p13.1) with schizophrenia and related disorders in one large pedigree. Additional families providing similarly positive evidence are required before linkage to D5S111 can be considered established. However, it is possible that, similar to some other diseases where genetic subtypes have been found, the marker we examined at the D5S111 locus identifies a rare genetic variety of schizophrenia and related disorders. In bipolar disorder, for example, a recent study found similarly provocative evidence for linkage in one of 47 families of bipolar disorder probands on chromosome 21 [Straub et al., 1994]. More definitively, in Alzheimer's disease, a point mutation at codon 717 of the amyloid precursor protein gene on chromosome 21 among others has been conclusively identified, but only in a very small number of families [Chariter Harlin et al., 1991]. A gene accounting for a variety of schizophrenia and related disorders, if identified, would potentially have important heuristic value even if it was extremely rare.

It may be of significance that family 17 has its origins in a relatively isolated rural area of Puerto Rico. Inward migration to this longstanding impoverished region, even among Puerto Ricans from other parts of the island, has been rare for many prior generations, when the population of this region was small [Vazquez Calzada, 1981]. It is thus possible that the variety of schizophrenia and related disorders present in this family may have arisen from a genetic variant of schizophrenia that is both local to and more ubiquitous in this region. Thus, this finding offers a testable hypothesis for linkage studies of schizophrenia and related disorders in relatively large informative families with ancestry from the same region.

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REFERENCES

American Psychiatric Association (1987): "Diagnostic and Statistical Manual of Mental Disorders, 3rd Rev. Ed." Washington, DC: American Psychiatric Association.

American Psychiatric Association (1994): "Diagnostic and Statistical Manual of Mental Disorders, 4th Edition." Washington, DC: American Psychiatric Association.

Andreasen NC (1985): "Comprehensive Assessment of Symptoms and History (CASH)." Iowa City, IA: The University of Iowa.

Andreasen NC, Endicott J, Spitzer RL, Winokur G (1977): The family history method using diagnostic criteria: Reliability and validity. Arch Gen Psychiatry 34:1229–1235.

Aschauer HN, Aschauer-Treiber G, Isenberg KE, Todd RD, Knesevich MA, Garver DL, Reich T, Cloninger CR (1990): No evidence for linkage between chromosome 5 markers and schizophrenia. Hum Hered 40:109–115.

Baron M, Gruen R, Asnis L, Kane J (1982): Schizoaffective illness, schizophrenia, and affective disorders: Morbidity risk and genetic transmission. Acta Psychiatr Scand 65:253–262.

Baron M, Gruen R, Rainer JD, Kane J, Asnis L, Lord S (1985): A family study of schizophrenia and normal probands: Implications for the spectrum concept of schizophrenia. Am J Psychiatry 142: 447–455.

Bassatt AJ, McGillivray BC, Jones BD, Pantzar JT (1988): Partial trisomy 5 cosegregating with schizophrenia. Lancet 9:799–801.

Chartier Harlin MC, Crawford F, Houlden H, Warren A, Hughes D, Fidani L, Goate A, Rossor M, Roques P, Hardy J, Mullan M (1991): Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. Nature 353:844–846.

Coon H, Jensen S, Holik J, Hoff M, Myles-Worsley M, Reimherr F, Wender PH, Waldo M, Freedman R, Leppert M, Byerly W (1994): Genomic scan for genes predisposing to schizophrenia. Am J Med Genet (Neuropsych Gen) 54:59–71.

Cornblatt BA, Erlenmeyer-Kimling L (1985): Global attentional deviance as a marker of risk for schizophrenia: Specificity and predictive validity. J Abnorm Psychol 94:470–486.

Curtis D, Gurling H (1993): A procedure for combining 2-point lod scores into a summary multipoint map. Hum Hered 43:173–185.

Detera-Wadleigh SD, Goldin LR, Sherrington R, Encio R, de Miguel C, Berrettini W, Gurling H, Gershon ES (1989): Exclusion of linkage to 5q11-13 in families with schizophrenia and other psychiatric disorders. Nature 340:391–393.

Durner M, Greenberg DA (1995): Phenocopies vs. genetic heterogeneity: Can we use phenocopy frequencies in linkage analysis to compensate for heterogeneity. Human heredity, in press.

Endicott J, Spitzer RL (1978): A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 35:837–844.

Frangos E, Athanassenas G, Tsitouorides S, Katsanou N, Alexandrakou P (1985): Prevalence of DSM-III schizophrenia among first-degree relatives of schizophrenic probands. Acta Psychiatr Scand 72: 382–386.

Freimer NB, Sargeant M, Breitner JCS (1993): Incorrect specification of marker allele frequencies: Effects on linkage analysis. Am J Med Genet 52:1102–1110.

Gershon ES, DeLisi LE, Hamovit J, Nurnberger JI, Maxwell MD, Schreiber J, Dauphinais D, Dingman CW, Guroff JJ (1988): A controlled family study of chronic psychoses. Arch Gen Psychiatry 45:328–336.

Greenberg DA, Berger B (1994): Using lod-score differences to determine mode of inheritance: A simple, robust, method even in the presence of heterogeneity and reduced penetrance. Am J Hum Genet 55:834–840.

Grove WM, Lebow BS, Clementz BA, Cerri A, Carlota M, Iacono WG (1991): Familial prevalence and coaggregation of schizotypy indicators: A multitrait family study. J Abnorm Psychol 100:115–121.

Gunderson JG, Siever LJ, Spaulding E (1983): The search for the schizotype: Crossing the border again. Arch Gen Psychiatry 40: 15–22.

Gurling H (1994): Genetic linkage analysis: A critical appraisal of the resolution of heterogeneity in the schizophrenias. In Gershon ES, Cloninger CR (eds): "Genetic Approaches to Mental Disorders." Washington, DC: American Psychiatric Press, Inc., pp 231–252.

Hallmayer J, Maier W, Ackenheil M, Ertl MA, Schmidt S, Minges J, Lichterman D, Widenauer D (1992): Evidence against linkage of schizophrenia to chromosome 5q11-5q13 markers in systematically ascertained families. Biol Psychiatry 31:83–94.

Hodge SE, Elston RC (1994): Lods, wrods, and mods: The interpretation of lod scores calculated under different models. Genet Epidemiol 11:329–342.

Hodge SE, Greenberg DA (1992): Sensitivity of lod scores to changes in diagnostic status. Am J Hum Genet 50:1053–1066.

Holzman PS, Kringlen E, Matthysse S, Flanagan SD, Lipton RB, Cramer G, Levin S, Lange K, Levy DL (1988): A single dominant gene can account for eye tracking dysfunctions and schizophrenia in offspring of discordant twins. Arch Gen Psychiatry 45:641–647.

Ingraham LJ (1995): Family-genetic research and schizotypal personality. In Raine A, Lencz T (eds): "Schizotypal Personality." Cambridge, UK: Cambridge University Press, pp 19–42.

Kaufman CA, DeLisi LE, Lehner T, Gilliam TC (1989): Physical mapping, linkage analysis of a putative schizophrenia locus on chromosome 5q. Schizophr Bull 15:441–452.

Keefe RSE, Silverman JM, Cornblatt B, Siever LJ (1991): Refining the phenotype for schizophrenia linkage studies. Soc Biol 38:197–218.

Kendler KS (1985): Diagnostic approaches to schizotypal personality disorder: A historical perspective. Schizophr Bull 11:538–553.

Kendler KS (1988): Familial aggregation of schizophrenia and schizophrenia spectrum disorders: Evaluation of conflicting results. Arch Gen Psychiatry 45:377–383.

Kendler KS (1989): The Structured Interview for Schizotypy (SIS): A preliminary report. Schizophr Bull 15:559–571.

Kendler KS, Diehl SR (1993): The genetics of schizophrenia: A current genetic-epidemiologic perspective. Schizophr Bull 19:261–285.

Kendler KS, Gruenberg AM (1984): An independent analysis of the Copenhagen sample of the Danish Adoption Study of Schizophrenia: VI. The relationship between psychiatric disorders as defined by DSM-III in the relatives and adoptees. Arch Gen Psychiatry 41:555–564.

Kendler KS, Gruenberg AM, Kinney DK (1994): Independent diagnoses of adoptees and relatives as defined by DSM-III in the Provincial and National samples of the Danish Adoption Study of Schizophrenia. Arch Gen Psychiatry 51:456–468.

Kendler KS, Gruenberg AM, Strauss JS (1981a): An independent analysis of the Copenhagen sample of the Danish Adoption Study of Schizophrenia: I. The relationship between anxiety disorder and schizophrenia. Arch Gen Psychiatry 38:973–977.

Kendler KS, Gruenberg AM, Strauss JS (1981b): An independent analysis of the Copenhagen sample of the Danish Adoption Study of Schizophrenia: II. The relationship between schizotypal personality disorder and schizophrenia. Arch Gen Psychiatry 38: 982–987.

Kendler KS, Gruenberg AM, Strauss JS (1982): An independent analysis of the Copenhagen sample of the Danish Adoption Study of Schizophrenia: IV. The relationship between major depressive disorder and schizophrenia. Arch Gen Psychiatry 39:639–642.

Kendler KS, Gruenberg AM, Tsuang MT (1985): Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients: A family study using DSM-III criteria. Arch Gen Psychiatry 42: 770–779.

Kendler KS, Gruenberg AM, Tsuang MT (1986): A DSM-III family study of the non-schizophrenic psychotic disorders. Am J Psychiatry 143:1098–1105.

Kendler KS, Masterson CC, Ungaro R, Davis KL (1984): A family history study of schizophrenia-related personality disorders. Am J Psychiatry 141:424–427.

Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D (1993a): The Roscommon Family Study. I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. Arch Gen Psychiatry 50:527–540.

Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D (1993b): The Roscommon Family Study. IV. Affective illness, anxiety disorders, and alcoholism in relatives. Arch Gen Psychiatry 50:952–960.

Kendler KS, McGuire M, Gruenberg AM, Spellman M, O'Hare A, Walsh D (1993c): The Roscommon Family Study: III. Schizophrenia-related personality disorder in relatives. Arch Gen Psychiatry 50:781–788.

Kendler KS, McGuire M, Gruenberg AM, Spellman M, O'Hare A, Walsh D (1993d): The Roscommon Family Study. II. The risk of nonschizophrenic nonaffective psychoses in relatives. Arch Gen Psychiatry 50:645–652.

Kendler KS, Ochs AL, Gorman AM, Hewitt JK, Ross DE, Mirsky A (1991): The structure of schizotypy: A multitrait twin study. Psychiatry Res 36:19–36.

Kennedy JL, Giuffra LA, Moises HW, Cavalli-Sforza LL, Pakstis AJ, Kidd JR, Castiglione CM, Sjogren B, Wetterberg L, Kidd KK (1988): Evidence against linkage of schizophrenia to markers on chromosome 5 in a northern Swedish pedigree. Nature 336: 167–170.

Kennedy JL, Giuffra LA, Moises HW, Wetterberg L, Sjogren B, Cavalli-Sforza LL, Pakstis AJ, Kidd JR, Kidd KK (1989): Molecular genetic studies in schizophrenia. Schizophr Bull 15:383–391.

Kety SS, Rosenthal D, Wender PH, Schulsinger F, Jacobsen B (1975): Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic: A preliminary report based on psychiatric interview. In Fieve R, Rosenthal D, Brill H (eds): "Genetic Research in Psychiatry." Baltimore: Johns Hopkins Press, pp 147–165.

Lahiri DK, Nurnberger JL (1991): A rapid non-enzymatic method for the preparation of HMW DNA from blood from RFLP studies. Nucleic Acid Res 19:5444–5449.

Macciardi F, Kennedy JL, Ruocco L, Giuffra L, Carrera P, Marino C, Rinaldi V, Smeraldi E, Ferrari M (1992): A genetic linkage study of schizophrenia to chromosome 5 markers in a northern Italian population. Biol Psychiatry 31:720–728.

Maier W, Lichterman D, Minges J, Hallmayer J, Heun R, Benkert O, Levinson DF (1993): Continuity and discontinuity of affective disorders and schizophrenia: Results of a controlled family study. Arch Gen Psychiatry 50:871–883.

Maier W, Lichtermann D, Minges J, Heun R (1994): Personality disorders among the relatives of schizophrenic patients. Schizophr Bull 20:481–493.

Malaspina D, Warbuton D, Amador X, Harris M, Kaufman CA (1992): Association of schizophrenia and partial trisomy of chromosome 5p: A case report. Schizophr Res 7:191–196.

McGuffin P, Sargeant M, Hetti G, Tidmarsh S, Whatley S, Marchbanks RM (1990): Exclusion of a schizophrenia susceptibility gene from the chromosome 5q11-q13 region: New data and a reanalysis of previous reports. Am J Hum Genet 47:524–535.

Onstad S, Skre I, Edvardsen J, Torgersen S, Kringlen E (1991): Mental disorders in first-degree relatives of schizophrenics. Acta Psychiatr Scand 83:463–467.

Ott J (1985): A complete program for linkage analysis of general human pedigrees. Am J Hum Genet 28:528–529.

Sherrington R, Brynjolfsson J, Petursson H, Potter M, Dudleston K, Barraclough B, Wasmuth J, Dobbs M, Gurling H (1988): Localization of a susceptibility locus for schizophrenia on chromosome 5. Nature 336:164–167.

Siever LJ, Bernstein DP, Silverman JM (1996): Schizotypal personality disorder. In Widiger T, Frances AJ, Pincus HA, Ross R, First MB, Davis WW (eds): "DSM-IV Sourcebook, Vol. 2." Washington, DC: American Psychiatric Press, pp. 685–702.

Silverman JM, Pinkham L, Horvath TB, Coccaro EF, Klar H, Schear S, Apter S, Davidson M, Mohs RC, Siever LJ (1993): Schizophrenia-related and affective personality disorder traits in relatives of schizophrenic and personality disorder probands. Am J Psychiatry 150:435–442.

Silverman JM, Siever LJ, Zanarini MC, Coccaro EF, Mitropoulou V (1995): Report on the proposed criteria for schizotypal personality disorder. In Widiger T (ed): "DSM-IV Sourcebook Vol. 4." Washington, DC: American Psychiatric Press.

Spitzer R, Endicott J, Gibbon M (1979): Crossing the border into borderline personality disorder and borderline schizophrenia: The development of criteria. Arch Gen Psychiatry 36:17–24.

Spitzer RL, Endicott J, Robins E (1972): "Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, 3rd ed." New York: New York State Department of Mental Hygiene Biometrics Research.

Squires-Wheeler E, Skodol E, Friedman D, Erlenmeyer-Kimling L (1988): The specificity of DSM-III schizotypal personality traits. Psychol Med 18:757–765.

Stangl D, Pfohl B, Zimmerman M (1985): A structure interview for the DSM-III personality disorders. Arch Gen Psychiatry 42:591–596.

St. Clair D, Blackwood D, Muir W, Baillie D, Hubbard A, Wright A, Evans HJ (1989): No linkage of chromosome 5q11-q13 markers to schizophrenia in Scottish families. Nature 339:305–309.

Straub RE, Lehner T, Luo Y, Loth JE, Shao W, Sharpe L, Alexander JR, Das K, Simon R, Fieve RR, Lerer B, Endicott J, Ott J, Gilliam TC, Baron M (1994): A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. Nature Genet 8: 291–296.

Torgersen S, Onstad S, Skre I, Edvardsen J, Kringlen E (1993): "True" schizotypal personality disorder: A study of co-twins and relatives of schizophrenic probands. Am J Psychiatry 150:1661–1667.

Vazquez Calzada JL (1981): La distribucion geografica de la poblacion de Puerto Rico. Rev Ciencias Soc 23:93–123.

Webb CT, Levinson DF (1993): Schizotypal and paranoid personality disorder in the relatives of patients with schizophrenia and affective disorders: A review. Schizophr Res 11:81–92.

Weber JL, Polymeropoulos MH, May PE, Kwitek AE, Xiao H, McPherson JD, Wasmuth JJ (1991): Mapping of human chromosome 5 microsatellite DNA polymorphisms. Genomics 11:695–700.

Weissenbach J, Gyapay G, Dib C, Vignal A, Morisette J, Millasseau P, Vaysseiz G, Lathrop M (1992): A second-generation linkage map of the human genome. Nature 359:794–801.

Weissman MM, Gershon ES, Kidd KK, Prusoff BA, Leckman JF, Dibble E, Hamovit J, Thompson WD, Pauls DL, Guroff JJ (1984): Psychiatric disorders in the relatives of probands with affective disorders: The Yale University-National Institute of Mental Health Collaborative Study. Arch Gen Psychiatry 41:13–21.

Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I (1986): Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch Gen Psychiatry 43:923–929.